UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/693,056 | 10/24/2003 | Joost A. Kolkman | A-1217-US-CIP2 | 1550 |

30174 7590 01/24/2008

AMGEN INC.
1120 VETERANS BOULEVARD
SOUTH SAN FRANCISCO, CA 94080

| EXAMINER | |
|---|---|
| LIU, SUE XU | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1639 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 01/24/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/693,056 | KOLKMAN ET AL. | |
| | Examiner | Art Unit | |
| | Sue Liu | 1639 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10/31/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *95-107* is/are pending in the application.

4a) Of the above claim(s) *99,102,104 and 105* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *95-98,100,101,103,106 and 107* is/are rejected.

7)☒ Claim(s) *95* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/07 has been entered.

### *Claim Status*

2. Claims 1-94 have been cancelled.

Claims 95-107 are currently pending.

Claims 99, 102, 104 and 105 have been withdrawn.

Claims 95-98, 100, 101, 103, 106 and 107 are being examined in this application.

### *Election/Restrictions*

3. Applicants elected the following species:

(A) the following number of monomer domains: two

(B) the following specific sequence for the first monomer domain: CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSL;

(C) the following specific sequence for the second monomer domain: CQPDQFRCSSGRCLSREWLCDGEDDCEDDSDETDCPTRTSLQ;

(F) the following cells: bacterial cells;

(G) the following first target molecule: IgE;

(H) the following second target molecule: IgE;

in the Reply filed on 10/16/06 is as previously acknowledged.

***Priority***

4. This application is a CIP of 10/289,660 (filed on 11/06/2002; now ABN), which is a CIP of 10/133,128 (filed 04/26/2002), which claims benefit of the following provisional applications:

60/374,107 04/18/2002;

60/333,359 11/26/2001;

60/337,209 11/19/2001;

60/286,823 04/26/2001.

5. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention, which is also disclosed, in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/286,823, filed on 4/26/01, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. For examples, the '823 provisional patent does not provide support for LDL-receptor Class A domain and the consensus sequence such as the one depicted by SEQ ID NO:331. The current application obtains the priority date of 60/337,209.

Thus, the effective filing date of the instant application is 11/19/01.

***Claim Objection(s) / Rejection(s) Withdrawn***

6. In light of applicants' amendments to the claims and supporting arguments, the following claim rejection as set forth in the previous office action is withdrawn:

Claims 95-98, 100, 101, 103, 106 and 107 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. In light of applicants' amendments to the claims to recite "each of the first and second LDL-receptor class A monomer domain variants consists of an amino acid sequence that is not present in any naturally-occurring A monomer domain" and supporting arguments (Reply, pp.7-9), the following claim rejection as set forth in the previous office action is withdrawn:

Claims 95, 100, 103, 106 and 107 are rejected under 35 U.S.C. 102(b) as being anticipated by Esser et al (Journal of Biological Chemistry. Vol. 263: 13282-13290; 1988).

8. In light of applicant's cancellation of the conflicting claims in the copending application, 10/971679, the following ODP rejection is withdrawn:

Claim 95-98 and 103 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21, 22, 24, 25, and 31 of copending Application No. 10/971,679 (20050164301; filed 10/22/04).

***Claim Rejections Maintained***

***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

*Esser, Bajari, Russell and Rudolph*

10. Claims 95-98, 100, 101, 103, 106 and 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Esser et al (Journal of Biological Chemistry. Vol. 263: 13282-13290; 1988; cited previously), in view of Bajari et al (Biological Chemistry. Vol. 379: 1053-1062; Aug/Sept.,

1998; cited previously), and if necessary further in view of Russell et al (Journal of Biological Chemistry. Vol. 264 (36): 21682-21688; 1989; cited previously), and Rudolph et al (The FASEB Journal. Vol. 10: p. 49-56; 1996; cited previously). The previous rejection is maintained for the reasons of record as set forth in the previous Office action as well as the reasons below.

Esser et al, throughout the publication, teach generation and analysis of mutant ligand binding domains (reading on LDL receptor class A monomer domains) of the human LDL lipoprotein receptor (Abstract).

The reference teaches recombinantly making the LDL receptor polypeptides using polynucleotides (plasmids) that encode for the said polypeptides and transformation in E. coli cells (p. 13283, right col.), which reads on the expression method of **clms 95**.

The reference teaches the consensus sequences and mutations of the cysteine-rich repeat regions of the ligand binding domain based on human wild-type sequence (see pg 13284, Figure 1), which the mutated repeats read on "LDL-receptor class A monomer domain" with "an amino acid sequence that is not present in any naturally occurring A monomer domain", as recited in **clm 95**, and the human monomer domain of **clm 106**. Each of the repeats listed in top panel of Figure 1 matches the consensus sequence of the instant **clm 95**. For example, the fifth repeat has 6 amino acid residues in between the first two C residues (which falls within the 3 to 15 range in the consensus); the repeat has 5 residues in between the 2nd and 3rd C residues (which falls within the 4 to 15 range in the consensus); the repeat has 6 residues in between 3rd and 4th C residues (which falls within the 6 to 7 range); the repeat has a D residue after the 4th C residue, followed by 3 residues, and another D residue (which matches the consensus sequence requirement); the repeat has 4 residues after the 5th C residue, followed by a D, an E, and

another two residues (which falls within the requirement of the consensus sequence). The reference also teaches that the wildtype human sequence (or naturally occurring sequence) is mutated at various positions. For example, the protein mutation construct with a point mutation at $Phe^{181}$→Gly position in "repeat 5" (i.e. one LDL-receptor class A monomer domain) can be considered to "consist of an amino acid sequence that is not present in any naturally-occurring A monomer domain" as recited in **clm 95**.

The reference also teaches linkers in between the repeats (or monomers) as indicated in Figures 1 and 2, which read on the 1-20 amino acids heterologous linker of **clms 95** and **107**.

The reference also teaches that the LDL receptor binds to various ligands (such as ApoB-100 of LDL and ApoE) through the cysteine-rich repeat regions (corresponding to the LDL receptor class A monomer domains), which reads on the monomer domains have a binding specificity for a target molecule of **clm 95.**

The reference teaches the polypeptides comprising the monomer domains are expressed in cells in the form of binding proteins (p. 13283-13284, bridging para.), which reads on the step of submitting the polypeptide to conditions that refold the polypeptide of **clm 100** because the polypeptides taught by the reference are properly folded into binding proteins.

The reference teaches the different polypeptides have different binding specificity to different ligands (see Abstract, Tables I and II, and pg13287+ of the reference), which reads on the limitations of **clm 103.**

Although the reference does not explicitly teach expressing a polypeptide comprising two A monomer domains where both of the domains have mutations in the amino acid sequence relative to the wildtype sequence, it would have been prima facie obvious for one of ordinary

skill in the art at the time the invention was made to make polypeptides comprising two mutant A monomer domains relative to the naturally occurring wildtype monomer sequences.

A person of ordinary skill in the art would have been motivated at the time of the invention to mutate two repeats (or A monomer domains) within the LDL receptor binding domain, because Esser et al teach the motivation to make mutations such as to study the various binding properties of the LDL receptor. Esser et al also teach that mutations within the various "repeats" or A monomer domains result in polypeptides with different ligand binding properties. (e.g. Table 1, p.13286). For example, the Phe181→Gly mutation in repeat five produced increased IgG binding ability for the resulted protein. Thus, one of ordinary skill in the art would have been motivated at the time of the invention to mutate additional "repeats" or A monomer domains to alter (increase or decrease) the binding properties of the LDL receptor protein for various applications. In addition, it would have been obvious to one of ordinary skill in the art to make additional mutations in multiple repeats (or A monomer domains) of the LDL receptor protein, because using known techniques such as protein mutagenesis for producing mutant proteins to provide proteins with altered (or improved) binding properties of the mutant polypeptides taught by the Esser reference would have been obvious to one of ordinary skill. See *KSR, 127 S.Ct. at 1741, 82 USPQ2d at 1396.*

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since generating protein mutations in a given protein is known and routine in the art, and the wildtype sequences of the LDL receptor A monomer domains are known in the art as taught by Esser et al.

Esser et al also do not explicitly teach using bacteria phage display to express the LDL receptor A domain polypeptides as recited in **clms 96-98**. The reference also does not teach the method step of dialyzing the polypeptide as recited in **clm 101**.

However, Bajari et al, throughout the publication, teach using phage display to screen for LDL receptor A domain (LR8 fragments) or variants thereof that bind to a protein target (see Abstract). The reference teaches expression of the polypeptides using phage display technology by employing MC1061 cells (*E. coli* cells) (p. 1059, para 1), which reads on the bacteriophage display recited in **clms 96-98**. The reference also teaches the standard protein purification step of dialysis after protein elution (p. 1060, 2nd para), which reads on the dialysis step of **clm 101**. The reference further teaches the advantage of using phage display, because it provides a powerful tool to manipulate (mutate) the LDL receptor A domains so that the receptor's ligand binding property can be altered for various purposes such as diagnostics or therapeutic interests (Abstract of the reference).

Russell et al, throughout the publication, teach mutational analysis of LDL receptor A domains (the monomer repeats) (see Abstract). The reference also teaches mutations of the LDL receptor A domains can lead to different ligand binding specificity and affinity (p. 21687, last para). The reference also teaches that the multiplicity of ligand binding repeats in the LDL receptor is necessary to all the receptor to bind to different ligands, and binding of each of the different ligands require interaction with different combinations of the repeats.

Rudolph et al, throughout the publication, teach in vitro folding of inclusion body proteins that are produced from recombinant protein expression (see Abstract). The reference

teaches the need to dialyze the isolated proteins that are expressed recombinant, because the dialysis is usually required for proper refolding of isolated proteins (p. 51, right col., 2nd para).

A person of ordinary skill in the art would have been motivated at the time of the invention to use bacteriophage display system to express libraries of polypeptides that need to be screened, because bateriophage display system provides a powerful tool to manipulate (mutate) the LDL receptor monomer domains for various purposes, as discussed above. In addition, Rudolph et al also teaches the need to mutate the different repeats (or monomers) of the LDL receptor domain for generation of LDL receptor with various binding specificity, as discussed above.

A person of ordinary skill in the art would have been motivated at the time of the invention to dialyze the isolated recombinant protein for subsequent assays, because Rudolph et al has demonstrated the need for dialysis step so that the isolated protein can be proper refolded, as discussed above.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since Bajari et al have demonstrated the success of expressing polypeptides with mutant LDL receptor repeats, and both Bajari and Rudolph et al have demonstrated the standard dialysis step in recombinant protein purification procedure is known and routine in the art.

*Discussion and Answer to Argument*

11. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

*Applicants argue that the above cited references do not teach all elements of the claimed invention. (Reply, pp. 9-14).*

Applicants made the above assertion by attacking each of the cited reference individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

*Applicants also seem to argue that none of the cited references teach "mutations" in at least two "Repeats" (or monomer domains). (Reply, pp. 9-14).*

Applicants are respectively directed to the body of the above rejection for discussion of how the cited references render the instant claimed invention obvious.

*Applicants also assert that "the Examiner has not articulated any reasoning or rationale why one of skill in the art would combine the disparate teachings of... to arrive at the claimed invention" (Reply, pp.13-14, bridging). Applicants also seem to argue that there is no motivation to combine the teaching of the references, and no motivation to generate mutations in multiple domains. (Reply, pp.12+)*

Applicants are respectively directed to the above rejection as well as reasons of record (presented in the previous Office actions) for discussions on motivation (or rationales) to combine the cited references. Furthermore, applicants are also respectively directed to the recent Supreme Court decision, which forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. *KSR, 127 S.Ct. at 1741, 82 USPQ2d at 1396.*

In addition, there is nothing in the cited references that teaches away from making mutations in multiple A monomer domains within a LDL receptor protein. As discussed above, for examples, the Esser reference teaches that certain mutations in the A monomer domains of the LDL receptor improve the ligand binding ability of the LDL receptor protein. Thus, one of the ordinary skill in the art would have been motivated to generate additional mutations to further improve (or alter) the binding ability of the LDL receptor protein.

The Russell reference also teaches mutations in different repeats (or A monomer domains) that created LDL receptor proteins with altered (decreased or increased) ligand binding abilities (e.g. p.21684, Figure 2; Table II). In addition, the Russell reference teaches the need to conduct further mutagenesis experiments (e.g. p.21687, col.2, para 1). The Russell reference also explicitly teaches "The current findings suggest that a multiplicity of cysteine-rich repeats may allow a single protein to bind several different protein ligands by employing different combinations of repeats" (Abstract). Thus, one of ordinary skill in the art would have been motivated to combine the different mutant "repeats" (or A monomer domains) from the Russell reference and/or Esser reference to arrive at LDL receptor proteins with different binding abilities that are capable of binding different ligands.

Thus, the cited combination of references clearly provides ample motivation to combine and arrive at the instant claimed invention.

### *New Claim Objection(s) or Rejection(s)*

### *Claim Objections*

12. Claim 95 is objected to because of the following informalities: The definite article, "the" in line 13 of claim 95 is misplaced in the claim language. Appropriate correction is required.

### *Claim Rejections - 35 USC § 103*

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

*Esser*

15. Claims 95, 100, 103, 106 and 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Esser et al (Journal of Biological Chemistry. Vol. 263: 13282-13290; 1988; cited previously). This rejection is necessitated by applicants' amendments to the claims.

The instant claims recite "a method for producing a polypeptide, said method comprising, expressing a nucleic acid encoding a polypeptide, thereby recombinantly expressing the polypeptide; wherein the polypeptide comprises a first LDL-receptor class A monomer domain variant and a second LDL-receptor class A monomer domain variant, wherein each of the first and second LDL-receptor class A monomer domain variants have consists of an amino acid sequence that is not present in any naturally-occurring A monomer domain, wherein the first and second LDL-receptor class A monomer domain variants each have a binding specificity for a target molecule, wherein the two domain variants are linked by a heterologous linker, and wherein each of first and second the LDL-receptor class A monomer domain variants comprise the following sequence:

**C**-$X_{(3-15)}$-**C**-$X_{(4-15)}$-**C**-$X_{(6-7)}$-**C**-[N,D]-$X_{(3)}$-[D,E,N,Q,H,S,T]-**C**-$X_{(4-6)}$-D-E-$X_{(2-8)}$-**C** (SEQ ID NO:331)".

Esser et al, throughout the publication, teach generation and analysis of mutant ligand binding domains (reading on LDL receptor class A monomer domains) of the human LDL lipoprotein receptor (Abstract).

The reference teaches recombinantly making the LDL receptor polypeptides using polynucleotides (plasmids) that encode for the said polypeptides and transformation in E. coli cells (p. 13283, right col.), which reads on the expression method of **clms 95**.

The reference teaches the consensus sequences and mutations of the cysteine-rich repeat regions of the ligand binding domain based on human wild-type sequence (see pg 13284, Figure 1), which the mutated repeats read on "LDL-receptor class A monomer domain" with "an amino

acid sequence that is not present in any naturally occurring A monomer domain", as recited in **clm 95**, and the human monomer domain of **clm 106**. Each of the repeats listed in top panel of Figure 1 matches the consensus sequence of the instant **clm 95**. For example, the fifth repeat has 6 amino acid residues in between the first two C residues (which falls within the 3 to 15 range in the consensus); the repeat has 5 residues in between the 2nd and 3rd C residues (which falls within the 4 to 15 range in the consensus); the repeat has 6 residues in between 3rd and 4th C residues (which falls within the 6 to 7 range); the repeat has a D residue after the 4th C residue, followed by 3 residues, and another D residue (which matches the consensus sequence requirement); the repeat has 4 residues after the 5th C residue, followed by a D, an E, and another two residues (which falls within the requirement of the consensus sequence). The reference also teaches that the wildtype human sequence (or naturally occurring sequence) is mutated at various positions. For example, the protein mutation construct with a point mutation at $Phe^{181}$→Gly position in "repeat 5" (i.e. one LDL-receptor class A monomer domain) can be considered to "consist of an amino acid sequence that is not present in any naturally-occurring A monomer domain" as recited in **clm 95**.

The reference also teaches linkers in between the repeats (or monomers) as indicated in Figures 1 and 2, which read on the 1-20 amino acids heterologous linker of **clms 95** and **107**.

The reference also teaches that the LDL receptor binds to various ligands (such as ApoB-100 of LDL and ApoE) through the cysteine-rich repeat regions (corresponding to the LDL receptor class A monomer domains), which reads on the monomer domains have a binding specificity for a target molecule of **clm 95.**

The reference teaches the polypeptides comprising the monomer domains are expressed in cells in the form of binding proteins (p. 13283-13284, bridging para.), which reads on the step of submitting the polypeptide to conditions that refold the polypeptide of **clm 100** because the polypeptides taught by the reference are properly folded into binding proteins.

The reference teaches the different polypeptides have different binding specificity to different ligands (see Abstract, Tables I and II, and pg13287+ of the reference), which reads on the limitations of **clm 103.**

Although the reference does not explicitly teach expressing a polypeptide comprising two A monomer domains where both of the domains have mutations in the amino acid sequence relative to the wildtype sequence, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to make polypeptides comprising two mutant A monomer domains relative to the naturally occurring wildtype monomer sequences.

A person of ordinary skill in the art would have been motivated at the time of the invention to mutate two repeats (or A monomer domains) within the LDL receptor binding domain, because Esser et al teach the motivation to make mutations such as to study the various binding properties of the LDL receptor. Esser et al also teach that mutations within the various "repeats" or A monomer domains result in polypeptides with different ligand binding properties. (e.g. Table 1, p.13286). For example, the Phe181→Gly mutation in repeat five produced increased IgG binding ability for the resulted protein. Thus, one of ordinary skill in the art would have been motivated at the time of the invention to mutate additional "repeats" or A monomer domains to alter (increase or decrease) the binding properties of the LDL receptor protein for various applications. In addition, it would have been obvious to one of ordinary skill in the art to

make additional mutations in multiple repeats (or A monomer domains) of the LDL receptor protein, because using known techniques such as protein mutagensis for producing mutant proteins to provide proteins with altered (or improved) binding properties of the mutant polypeptides taught by the Esser reference would have been obvious to one of ordinary skill. See *KSR, 127 S.Ct. at 1741, 82 USPQ2d at 1396.*

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since generating protein mutations in a given protein is known and routine in the art, and the wildtype sequences of the LDL receptor A monomer domains are known in the art as taught by Esser et al.

***Double Patenting***

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 95 and 103 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 93 and 108 of copending Application No. 10/133,128 (US 20030082630; hereinafter referred to as the '128 application) in view of Esser et al (Journal of Biological Chemistry. Vol. 263: 13282-13290; 1988; cited previously). The '128 application claims a polypeptide comprising LDL-receptor class A monomer domain variants having amino acid sequences as recited in SEQ ID NO:201, which SEQ ID NO:201 is an exact match to SEQ ID NO:331 of the instant claim 95. The '128 application does not specifically claim a method of producing the claimed polypeptide. The Esser reference teaches methods of producing various polypeptides comprising LDL receptor monomer domains (e.g. Abstract). Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to express a nucleic acid encoding the polypeptide comprising A monomer domains to produce the polypeptide. A person of ordinary skill in the art would have been motivated at the time of the invention to express the polypeptide using an encoding nucleic acid, because the Esser reference teaches it is routine and known in the art to produce polypeptides (encoding A monomer domains) from encoding nucleic acids and the expression methods offers the advantages of providing an convenient way of producing desired polypeptides.

It is also noted the "method of producing a polypeptide" of the instant claims does not read on any of the restricted method groups in the '128 application as the groups were set forth in the Restriction Requirement (mailed 9/29/04) of the '128 application. In addition, the instant application is also filed (10/24/03) before the restriction requirement of the '128 application. Thus, the prohibition again double patenting rejection does not apply. See MPEP 804.01.

This is a provisional obviousness-type double patenting rejection.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Sue Liu/
Patent Examiner, AU 1639
1/17/08